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29JAN04 E869059-1 002029
P01/7700 0.00-0401862.8 NONE

1.	Your Reference	PID/MM/PB60670P
2.	Patent application number *(The Patent office will fill in this part)*	2 8 JAN 2004 0401862.8
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB
	Patents ADP number *(if you know it)*	07358700 3
	If the applicant is a corporate body, give the country/state of its corporation	GB
4	Title of the invention	USE OF COMBINATIONS OF PYRAZOLO[1,5-B]PYRIDAZINE DERIVATIVES AND PYRIMIDINE DERIVATIVES WITH SSRI INHIBITORS FOR THE TREATMENT OF DEPRESSIVE DISORDERS
5	Name of your agent *(if you know one)*	PETER DOLTON
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY (CN9 25.1) 980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS
	Patents ADP number *(if you know it)*	80725550 04

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year).

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.

YES

ote (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Description	11
Claim(s)	3
Abstract	2
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

P. C. Dolton

Signature PETER DOLTON 28 January 2004
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

AMANDA WILKINSON

020 8047 4493

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PB60670P

USE OF COMBINATIONS OF PYRAZOLO[1,5-B]PYRIDAZINE DERIVATIVES AND PYRIMIDINE DERIVATIVES WITH SSRI INHIBITORS FOR THE TREATMENT OF DEPRESSIVE DISORDERS

Depression is a chronic disease that affects persons of all ages. In the Diagnostic and Statistical Manual of Mental disorders, Fourth Edition, (DSM IV published by the American Psychiatric Association, depressive disorders are classified under mood disorders and are divided into three types: major depressive disorder, dysthymic disorder and depressive disorder not otherwise specified. Major depressive disorder and dysthymic disorder are differentiated based on chronicity, severity and persistence. In major depression, the depressed mood must be present for two weeks. In dysthymic disorder, the depressed mood must be present for two weeks. In dysthymic disorder the depressed mood must be present most days over a period of two years. Usually, major depressive disorder is characterized by its sharp contrast to usual functioning. A person with a major depressive episode can be functioning and feeling normal and suddenly develop severe symptoms of depression. By contrast, a person with dysthymic disorder has chronic depression with less severe symptoms than major depression.

In an effort to treat depression, a variety of antidepressant compositions have been developed. Among these the selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) have become first choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

However, clinical studies on depression indicate that non- response to SSRIs is substantial, up to 30%. Another, often neglected, factor in antidepressant treatment is compliance, which has a rather profound effect on the patient's motivation to continue pharmacotherapy.

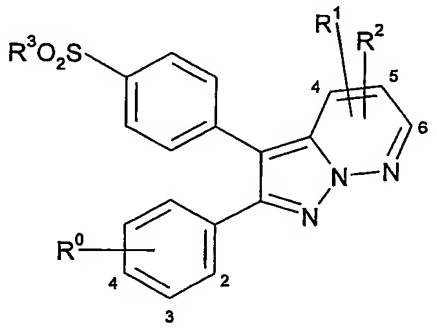
First of all, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Secondly, sexual dysfunction is a side effect common to all SSRIs. Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

Accordingly, the development of an antidepressant capable of exhibiting its effect rapidly is desired.

The invention provides a method for treating a patient suffering from or susceptible to psychiatric disorders as defined above comprising administering to said patient an effective amount of a first component which is a COX-2 inhibitor, in combination with an effective amount of a second component which is a serotonin reuptake inhibitor.

In the general expressions of the present invention, the first component is a compound which acts as a COX-2 inhibitor.

The COX-2 inhibitors of the present invention include, but are not limited to, the following pyrazolo[1,5-b]pyridazine derivatives of formula (I), as disclosed in WO 99/12930, which is herein incorporated by reference.

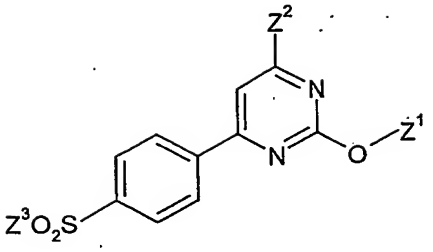


(I)

and pharmaceutically acceptable derivatives thereof in which:

R^0	is halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more fluorine atoms, or $O(CH_2)_nNR^4R^5$;
R^1	is selected from H, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more fluorine atoms, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, SC_{1-6}alkyl, C(O)H, $C(O)C_{1-6}$alkyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$alkyl, $O(CH_2)_nSC_{1-6}$alkyl, $(CH_2)_nNR^4R^5$, $(CH_2)_nSC_{1-6}$alkyl or $C(O)NR^4R^5$;
	with the proviso that when R^0 is at the 4-position and is halogen, at least one of R^1 and R^2 is C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$alkyl, $O(CH_2)_nSC_{1-6}$alkyl, $(CH_2)_nNR^4R^5$ or $(CH_2)_nSC_{1-6}$alkyl, $C(O)NR^4R^5$;
R^2	independently from R^1 has the same meanings;
R^3	is C_{1-6}alkyl or NH_2;
R^4 and R^5	are independently selected from H, or C_{1-6}alkyl or, together with the nitrogen atom to which they are attached, form a 4 - 8 membered saturated ring; and
n	is 1-4.

The COX-2 inhibitors of the present invention also include, but are not limited to, the following pyrimidine derivatives of formula (II), as disclosed in WO 02/096885, which is herein incorporated by reference:



(II)

in which:

Z^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-10}cycloalkylC_{0-6}alkyl, C_{4-12}bridged cycloalkyl, $A(CZ^4Z^5)n$ and $B(CZ^4Z^5)n$;

Z^2 is C_{1-2}alkyl substituted by one to five fluorine atoms;

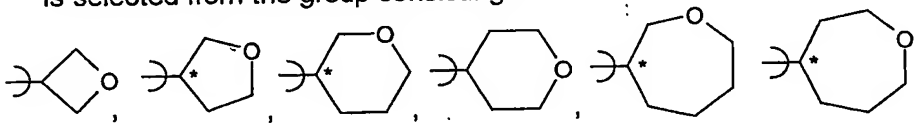
Z^3 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R_7CONH;

Z^4 and Z^5 are independently selected from H or C_{1-6}alkyl;

A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R_6;

Z^6 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and C_{1-6}alkylSO_2;

B is selected from the group consisting of



where) defines the point of attachment of the ring;

Z^7 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylOC_{1-6}alkyl, phenyl, HO_2CC_{1-6}alkyl, C_{1-6}alkyl$OCOC_{1-6}$alkyl, C_{1-6}alkylOCO, H_2NC_{1-6}alkyl, C_{1-6}alkyl$OCONHC_{1-6}$alkyl and C_{1-6}alkyl$CONHC_{1-6}$alkyl; and

n is 0 to 4.

The compounds of formula (I) and (II) preferred for use in the present invention are selected from the following group:

3-(4-methylsulfonyl-phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine;

6-difluoromethoxy-2-(4-fluoro-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]-pyridazine;

2-(4-ethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

2-(4-fluoro-phenyl)-6-methylsulfonyl-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

2-(4-difluoromethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

4-[2-(4-ethoxy-phenyl)-pyrazolo[1,5-b]pyridazin-3-yl]-benzenesulfonamide;

6-difluoromethoxy-2-(3-fluoro-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

2-(4-fluorophenoxy)-4-[4-(methylsulfonyl)phenyl]-6](trifluoromethyl)pyrimidine;
2-(4-methoxyphenoxy)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl)pyrimidine;
2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;
2-[(5-chloropyridin-3-yl)oxy]-4-[4-(methylsulfony)phenyl]-6-(trifluoromethyl)pyrimidine;
2-(cyclohexyloxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine.

The compounds, 2-(4-ethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]-pyridazine and 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt, are particularly preferred.

The preparation of the above compounds can be conveniently achieved as described in the International Patent Applications WO 99/12930 and WO 02/096885, which are herein incorporated by reference:

Similarly, when the invention is regarded in its broadest sense, the second component compound is a compound which functions as a selective serotonin reuptake inhibitor. The measurement of a compound's activity as an SSRI is now a standard pharmacological assay. Wong, et al., *Neuropsychopharmacology* 8, 337-344 (1993). Many compounds, including those discussed at length above, have such activity, and no doubt many more will be identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the protocol described by Wong supra.

Exemplary selective serotonin reuptake inhibitors include, but are not limited to: citalopram, escitalopram, fluoxetine, R-fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, duloxetine, dapoxetine, nefazodone, imipramine, imipramine N-oxide, desipramine, pirandamine, dazepinil, nefopam, befuraline, fezolamine, femoxetine, clomipramine, cianoimipramine, litoxetine, cericlamine, seproxetine, WY 27587, WY 27866, imeldine, ifoxetine, tiflucarbine, viqualine, milnacipran, bazinaprine, YM 922, S 33005, F 98214-TA, OPC 14523, alaproclate, cyanodothepine, trimipramine, quinupramine, dothiepin, amoxapine, nitroxazepine, McN 5652, McN 5707, VN 2222, L 792339, roxindole, YM 35992,0177, Org 6582, Org 6997, Org 6906, amitriptyline, amitriptyline N-oxide, nortriptyline, CL 255.663, pirlindole, indatraline, LY 113.821, LY 214.281, CGP 6085 A, RU 25.591, napamezole, diclofensine, trazodone, EMD 68.843, BMY 42.569, NS 2389, sercloremine, nitroquipazine, ademethionine, sibutramine, clovoxamine. The compounds mentioned above may be used in the form of the base or a pharmaceutically acceptable acid addition salt thereof.

Preferred selective serotonin reuptake inhibitors of the present invention include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3- phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Pat. No. 4,314,081 is an early reference on the compound. Robertson et al., *J. Med. Chem.*

31, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers;

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Pat. No. 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Pat. No. 4,761,501. Venlafaxine is identified as compound A in that patent;

Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Pat. No. 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., *Neuropharmacology* 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake;

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-aqscarbonitrile, is disclosed in U.S. Pat. No. 4,136, 193 as a serotonin reuptake inhibitor. Its pharmacology was disclosed by Christensen et al., *Eur. J. Pharmacol.* 41, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour et al., *Int. Clin. Psychopharmacol.* 2, 225 (1987), and Timmerman et al., ibid., 239;

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone-O-(2-aminoethyl)-oxime, is taught by U.S. Pat. No. 4,085,225. Scientific articles about the drug have been published by Claassen et al., *Brit. J. Pharmacol.* 60, 505 (1977); and De Wilde et al., *J. Affective Disord.* 4, 249 (1982); and Benfield et al., *Drugs* 32, 313 (1986);

Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Pat. Nos. 3,912,743 and 4, 007,196. Reports of the drug's activity are in Lassen, *Eur. J. Pharmacol.* 47, 351 (1978); Hassan et al., *Brit. J. Clin. Pharmacol.* 19, 705 (1985); Laursen et al., *Acta Psychiat. Scand.* 71, 249 (1985); and Battegay et al., *Neuropsychobiology* 13, 31 (1985);

Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro- N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor which is marketed as an antidepressant. It is disclosed by U.S. Pat. No. 4,536,518;

All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

It will be understood that while the use of a single COX-2 inhibitor of the present invention as a first component compound is preferred, combinations of two or more COX-2 inhibitors of the present invention may be used as a first component if necessary or desired. Similarly, while the use of a single selective serotonin reuptake inhibitor as a second component compound is preferred, combinations of two or more serotonin reuptake inhibitors may be used as a second component if necessary or desired.

While all combinations of first and second component compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

2-(4-ethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt as first component and paroxetine as second component.

In general, combinations and methods of treatment using a compound of formula (I) or (II) as the first component are preferred. Furthermore, combinations and methods of treatment using paroxetine as the second component are preferred. Especially preferred are combinations and methods of treatment using 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine as the first component and paroxetine as the second component.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p- bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate,

methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, b- hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here.

Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;
Duloxetine: from about 1 to about 160 mg once/day; or up to 80 mg twice daily; preferred, from about 5 to about 20 mg once/day;
Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day;
Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day;
Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day;
Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day;
Paroxetine: from about 20 to about 50 mg once/day; preferred, from about 20 to about 30 mg once/day;
Sertraline: from about 20 to about 500 mg once/day; preferred, from about 50 to about 200 mg once/day;

In more general terms, one would create a combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

The adjunctive therapy of the present invention is carried out by administering a first component together with the second component in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

The adjunctive combination may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one- third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

Depression/anxiety study

Activity of the compounds (I) and (II), in combination with SSRI inhibitors, vs. depression/anxiety may be evaluated according to the following models:

- Porsolt test in mouse for SSRI/TCA (tricyclic antidepressants) (Porsolt et al 1977, Arch Int Pharmacodyn Ther,: 229, 327-336);
- Chronic mild stress in rat for SSRI/TCA (Willner, 1991, TiPS,: 12, 131-136);
- Maternal deprivation in rat pups for SSRI (or modulator of serotonin receptors)/TCA (Gardner, 1985, J. Pharmacol. Methods 14: 181-187);
- Rat social interaction after chronic treatment with SSRI/TCA (File, 1980 J. Neurosci Methods, 2:219-238; Lightowler et al., 1994, Pharmacol., Biochem. Behaviour,: 49, 281-285);
- Gerbil social interaction after chronic treatment with SSRI (or modulator of serotonin receptors)/TCA (File, 1997, Pharmacol. Biochem. Behav. 58: 747-752).

Clinical Trials

The usefulness of the compound for treating a Depressive Disorder can be supported by the following studies as described.

Clinical Observations

A double-blind multicenter clinical trial may be designed to assess the safety and efficacy of a COX-2 inhibitor of the present invention in combination with an SSRI such as paroxetine for treatment of Bipolar Disorder, Bipolar Depression or Unipolar Depression. Patients are randomized to a COX-2 inhibitor, such as 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine an SSRI such as paroxetine or a COX-2 inhibitor plus an SSRI.

In one such study, an 8-week, double blind trial, 28 patients diagnosed with treatment-resistant major depression would be randomized to one of three treatment arms: (1) paroxetine:: and placebo; (2) . 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)-pyrimidine and placebo; or (3) paroxetine plus 2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine. The efficacy of the treatment may be monitored using the HAMD-21 (Hamilton M. *Journal of Neurology, Neurosurgery & Psychiatry.* 1960.23: 56-62, and Hamilton M. *Development of a rating scale for primary depressive illness.* British Journal of Social and Clinical Psychology. 1967; 6:278-296), Montgomery-Asberg Depression Rating Scale (MADRS)(Montgomery S A, Asberg M. *A new depression scale designed to be sensitive to change.* British Journal of Psychiatry. 1979;134:382-389), and the Clinical Global Impression (CGI)--Severity of Depression rating scale (Guy, W.

ECDEU Assessment Manual for Psychopharmacology. Revised ed. US Dept of Health, Education and Welfare, Bethesda, Md. 1976).

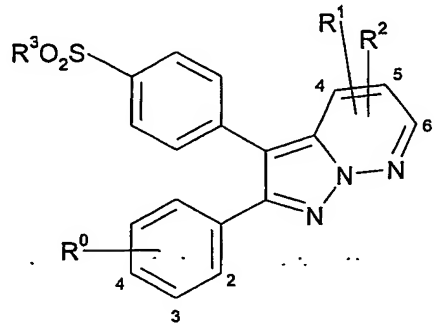
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A method for treating a patient suffering from or susceptible to Depressive Disorders comprising administering to said patient an effective amount of a first component which is a COX-2 inhibitor, selected in the group consisting of the following compounds of general formula (I) and (II):



(I)

and pharmaceutically acceptable derivatives thereof in which:

R^0 is halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more fluorine atoms, or $O(CH_2)_nNR^4R^5$;

R^1 is selected from H, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more fluorine atoms, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, SC_{1-6}alkyl, C(O)H, $C(O)C_{1-6}$alkyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$alkyl, $O(CH_2)_nSC_{1-6}$alkyl, $(CH_2)_nNR^4R^5$, $(CH_2)_nSC_{1-6}$alkyl or $C(O)NR^4R^5$;

with the proviso that when R^0 is at the 4-position and is halogen, at least one of R^1 and R^2 is C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$alkyl, $O(CH_2)_nSC_{1-6}$alkyl, $(CH_2)_nNR^4R^5$ or $(CH_2)_nSC_{1-6}$alkyl, $C(O)NR^4R^5$;

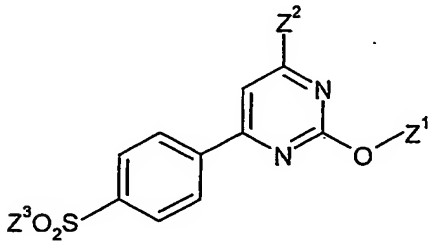
R^2 independently from R^1 has the same meanings;

R^3 is C_{1-6}alkyl or NH_2;

R^4 and R^5 are independently selected from H, or C_{1-6}alkyl or, together with the nitrogen atom to which they are attached, form a 4 - 8 membered saturated ring; and

n is 1-4;

and:



(II)

in which:

Z^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-10}cycloalkylC_{0-6}alkyl, C_{4-12}bridged cycloalkyl, A(CZ^4Z^5)n and B(CZ^4Z^5)n;

Z^2 is C_{1-2}alkyl substituted by one to five fluorine atoms;

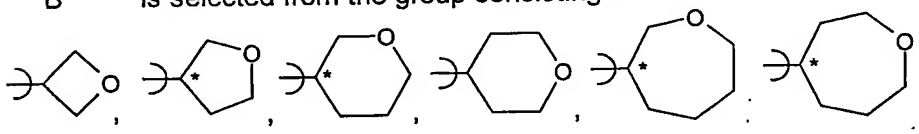
Z^3 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R_7CONH;

Z^4 and Z^5 are independently selected from H or C_{1-6}alkyl;

A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R_6;

Z^6 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and C_{1-6}alkylSO_2;

B is selected from the group consisting of



where) defines the point of attachment of the ring;

Z^7 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylOC_{1-6}alkyl, phenyl, HO_2CC_{1-6}alkyl, C_{1-6}alkyl$OCOC_{1-6}$alkyl, C_{1-6}alkylOCO, H_2NC_{1-6}alkyl, C_{1-6}alkyl$OCONHC_{1-6}$alkyl and C_{1-6}alkyl$CONHC_{1-6}$alkyl; and

n is 0 to 4;

in combination with an effective amount of a second component which is a selective serotonin reuptake inhibitor.

2. A method of claim 1 where the first component is selected from the group consisting of:

3-(4-methylsulfonyl-phenyl)-2-(4-methoxy-phenyl)-pyrazolo[1,5-b]pyridazine;

6-difluoromethoxy-2-(4-fluoro-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

2-(4-ethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

2-(4-fluoro-phenyl)-6-methylsulfonyl-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

2-(4-difluoromethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

4-[2-(4-ethoxy-phenyl)-pyrazolo[1,5-b]pyridazin-3-yl]-benzenesulfonamide;

6-difluoromethoxy-2-(3-fluoro-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine;

2-(4-fluorophenoxy)-4-[4-(methylsulfonyl)phenyl]-6](trifluoromethyl)pyrimidine;

2-(4-methoxyphenoxy)-4-[4-(methylsulfonyl)phenyl]-6-trifluoromethyl)pyrimidine;

2-butoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine;

2-[(5-chloropyridin-3-yl)oxy]-4-[4-(methylsulfony)phenyl]-6-(trifluoromethyl)pyrimidine;
2-(cyclohexyloxy)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine.

3. A method of claim 1 wherein the first component compound is 2-(4-ethoxy-phenyl)-3-(4-methylsulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine or 2-butoxy-4-[4-(methyl-sulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine or a pharmaceutical acceptable salt.

4. A method of claim 2 wherein the second component compound is paroxetine.

5. A method of claim 1 where administration of the compounds is oral.

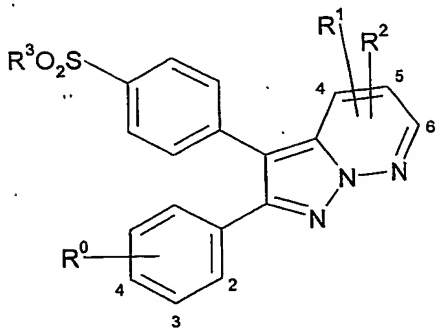
6. A method of claim 1 wherein the Depressive Disorder is Bipolar Disorder I.

7. A method of claim 1 wherein the Depressive Disorder is Bipolar Disorder II.

8. A pharmaceutical composition adapted for the treatment of a patient suffering from, or susceptible to bipolar disorder, bipolar depression or unipolar depression, comprising as the active ingredients a combination of the COX-2 inhibitors as defined in claim 1 and a second component selected from the group consisting of a serotonin reuptake inhibitor.

ABSTRACT

The invention concerns the use of compounds of formula (I) and formula (II)



(I)

and pharmaceutically acceptable derivatives thereof in which:

R^0 is halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more fluorine atoms, or $O(CH_2)_nNR^4R^5$;

R^1 is selected from H, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more fluorine atoms, C_{1-6}alkoxy, C_{1-6}hydroxyalkyl, SC_{1-6}alkyl, C(O)H, $C(O)C_{1-6}$alkyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$alkyl, $O(CH_2)_nSC_{1-6}$alkyl, $(CH_2)_nNR^4R^5$, $(CH_2)_nSC_{1-6}$alkyl or $C(O)NR^4R^5$;

with the proviso that when R^0 is at the 4-position and is halogen, at least one of R^1 and R^2 is C_{1-6}alkylsulphonyl, C_{1-6}alkoxy substituted by one or more fluorine atoms, $O(CH_2)_nCO_2C_{1-6}$alkyl, $O(CH_2)_nSC_{1-6}$alkyl, $(CH_2)_nNR^4R^5$ or $(CH_2)_nSC_{1-6}$alkyl, $C(O)NR^4R^5$;

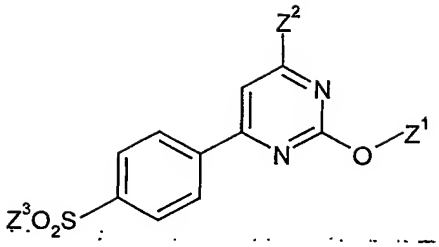
R^2 independently from R^1 has the same meanings;

R^3 is C_{1-6}alkyl or NH_2;

R^4 and R^5 are independently selected from H, or C_{1-6}alkyl or, together with the nitrogen atom to which they are attached, form a 4 - 8 membered saturated ring; and

n is 1-4;

and:



(II)

in which:

Z^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-10}cycloalkylC_{0-6}alkyl, C_{4-12}bridged cycloalkyl, A(CZ^4Z^5)n and B(CZ^4Z^5)n;

Z^2 is C_{1-2}alkyl substituted by one to five fluorine atoms;

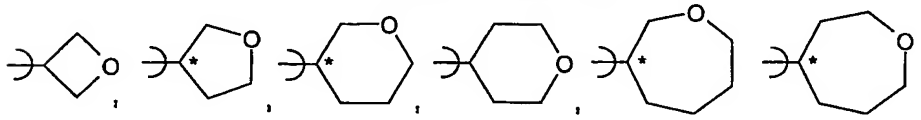
Z^3 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R_7CONH;

Z^4 and Z^5 are independently selected from H or C_{1-6}alkyl;

A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R_6;

Z^6 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and C_{1-6}alkylSO_2;

B is selected from the group consisting of



where) defines the point of attachment of the ring;

Z^7 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylOC_{1-6}alkyl, phenyl, HO_2CC_{1-6}alkyl, C_{1-6}alkyl$OCOC_{1-6}$alkyl, C_{1-6}alkylOCO, H_2NC_{1-6}alkyl, C_{1-6}alkyl$OCONHC_{1-6}$alkyl and C_{1-6}alkyl$CONHC_{1-6}$alkyl; and

n is 0 to 4;

which are COX-2 (cyclooxygenase-2) inhibitors, for the treatment of Depressive Disorders in combination with an effective amount of a second component which is a selective serotonin reuptake inhibitor.